Adjuvant systemic therapy in breast cancer: quo vadis?

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The premise that breast cancer (BC) has a tendency toward early systemic dissemination, together with empirical findings showing that drugs given after breast tumor surgery improve outcome, led to the development of systemic adjuvant therapy. This strategy, which started more than 50 years ago, revolutionized BC treatment and improved patient outcome in a substantial way. However, in recent years, several large trials that incorporated new systemic treatments in the adjuvant setting of BC failed to demonstrate a benefit. In the present review, we discuss the progress made in the adjuvant treatment of BC in the past decade, the possible reasons for the recent failures, and practical strategies that may be incorporated in the design of future trials.

Key words: breast cancer, adjuvant therapy, clinical trials, practical strategies

introduction

The history of systemic adjuvant treatment for breast cancer (BC) starts with tamoxifen, a selective estrogen receptor (ER) modulator that was developed during the 1960s and showed responses in patients with metastatic disease [1]. Thirty years later, a meta-analysis carried out by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) confirmed a 31% reduction in BC mortality in tamoxifen-treated patients [2]. More progress in systemic hormonal treatment occurred when aromatase inhibitors (AIs) (in postmenopausal women) and luteinizing hormone-releasing hormones (LHRH) agonists (in premenopausal women) were shown to be highly effective in ER-positive BC [3, 4]. During the 1980s, studies demonstrated that adjuvant chemotherapy regimens have a positive outcome on survival [5]. A meta-analysis of 194 studies conducted between 1985 and 2000 showed a 20%–38% reduction in BC mortality depending on the age of the patient [2]. Later on, at the beginning of the twenty-first century, it was shown that adding taxanes to an anthracycline-based control regimen further reduces BC mortality by an absolute 3%–4% at 8 years [6]. Trastuzumab (Herceptin®), a monoclonal antibody directed at the HER2/neu receptor, was the second targeted drug (after tamoxifen) that was incorporated into the adjuvant treatment of BC (only in HER2-positive disease): a number of randomized prospective clinical trials proved that its addition to chemotherapy decreased recurrence by 50% and mortality by 30% [7–10]. In the last few years, there has been an attempt to evaluate newer drugs in the adjuvant setting, such as lapatinib (a HER1/HER2 tyrosine kinase inhibitor) or bevacizumab [a monoclonal antibody against vascular endothelial growth factor (VEGF)], which have both demonstrated improved efficacy in advanced disease and/or in the neoadjuvant setting [11–15]. However, these attempts have failed. In the present review, we discuss the advances made in recent years, interesting questions for the future, and possible reasons for failure in incorporating new drugs into adjuvant treatment regimens for BC.

what is new in adjuvant BC treatment?

luminal cancers

Different multigene signatures are able to quantify the likelihood of distant recurrence and to predict the magnitude of chemotherapy benefit in women with ER-positive BC. All these assays identify a ‘low-risk’ group with very good prognosis, and the optimal adjuvant therapy for these patients should balance efficacy and toxicity [16–20]. In an attempt to reduce chemotherapy burden in adjuvant BC, Shulman et al. sought to determine whether single-agent paclitaxel was inferior to doxorubicin and cyclophosphamide when each was administered for four or six cycles of therapy, and whether it offered less toxicity. Most patients enrolled had lower risk (node-negative and two-thirds where ER-positive). This trial showed that single-agent paclitaxel was less toxic than doxorubicin and cyclophosphamide but was not able to demonstrate non-inferiority of paclitaxel [21].

Adjuvant therapy in ER-positive cancers with an AI provides better outcomes for postmenopausal patients than treatment with tamoxifen [22–26]. This finding led to the design of two phase 3 trials, TEXT and SOFT, which randomly assigned premenopausal women with ER-positive early BC to the AI exemestane plus ovarian suppression (to create a postmenopausal...
state) or to tamoxifen plus ovarian suppression for a period of 5 years. The patients enrolled in these studies had lower risk characteristics than those anticipated in the design assumptions, and the rate of disease-free survival (DFS) was better than expected. Therefore, in order to ensure timely answers to the trial questions, a protocol amendment planned for the combined analysis of TEXT and SOFT. After a median follow-up of 68 months, there was an absolute gain of 3.8% in DFS (from 87.3% to 91.1%) in the exemestane–ovarian suppression group compared with the tamoxifen–ovarian suppression group [27]. Overall survival (OS) at this point does not differ significantly between the two groups.

These trials provide a new treatment option to reduce the risk of recurrence for premenopausal women. However, a few concerns have been raised about TEXT and SOFT, which include the following: the long accrual period (2003–2011), the heterogeneous patient populations recruited (chemotherapy-treated versus not), and the fact that no OS benefit has yet been demonstrated. Another concern is the fact that the results of TEXT and SOFT contrast with the ones of the Austrian Breast and Colorectal Cancer Study Group-12 (ABC01-12) trial [28]. This trial showed a 3.2% absolute benefit for the addition of an adjuvant bisphosphonate (zoledronic acid), but no differences in the rate of DFS between patients who received anastrozole plus ovarian suppression and those who received tamoxifen plus ovarian suppression. The differences between the former trials and ABC01-12 may relate to differences in statistical power that favors the combined analysis of TEXT and SOFT, or to different treatment protocols. Of note, TEXT and SOFT did not permit the routine use of bisphosphonates.

The issue of adjuvant bisphosphonates is of separate interest: numerous studies that addressed this question were recently analyzed together in a pooled meta-analysis showing that adjuvant bisphosphonates led to a 3.1% absolute reduction in BC-related mortality, and a 2.3% decrease in all-cause mortality at 10 years in postmenopausal women [29].

Another emerging strategy in the treatment of luminal BC is extending adjuvant hormonal therapy to 10 years instead of 5. Two trials (aTTom and ATLAS) have demonstrated that continuing tamoxifen up to 10 years reduces the risk of BC recurrence and overall mortality; specifically, the reduction appears to be significant after year 10, suggesting that 10 years of tamoxifen treatment can approximately halve BC mortality during the second decade after diagnosis [30, 31]. The magnitude of benefit from such a strategy depends on tumor burden, biology, comorbidities, and patient age, and should be balanced against an increase in serious side-effects (endometrial cancer and thromboembolism) and quality-of-life alterations such as vasomotor symptoms, mood alterations, and sexual dysfunction. Whether adjuvant AIs need to be extended beyond 5 years is being addressed by several trials, but their results are pending.

**interesting questions for the future in luminal cancers.** Two major questions in the treatment of luminal BC will—be answered soon: (i) Can patients with intermediate genomic risk or discordant risk (low genomic risk/high clinical risk) be treated safely with endocrine therapy only? (ii) Will the manipulation of endocrine resistance using either CDK4/6 inhibitors/mTOR inhibitors (everolimus) further improve outcome? The first question should be addressed during 2015 or 2016, when the results of the TAILORx (NCT00310180) and the MINDACT (NCT00433589) trials will be reported. As for the second question, a number of phase 3 studies were recently launched using CDK4/6 inhibitors in addition to hormonal therapy in advanced disease [PALOMA-2 (NCT01740427), PALOMA-3 (NCT01942135), PEARL (NCT02028507), MONARCH2 (NCT02107703)] and a large adjuvant trial is being considered. Regarding mTOR inhibition to overcome endocrine resistance, the BOLETO-2 study provided compelling evidence of extended progression-free survival in the metastatic setting, although no OS benefit was achieved [32, 33]. This led to the design of two phase 3 adjuvant randomized, placebo-controlled trials: SWOG-S1207 (NCT01674140) and UNIRAD (NCT01805271), which are evaluating the addition of everolimus to adjuvant endocrine therapy for patients with high-risk ER-positive tumors.

**‘triple negative’ cancers**

‘Triple negative’ (ER-, PgR, and HER2-negative) breast cancers (TNBC), which account for 15%–20% of all invasive BC, still lack specific targets for therapy, despite extensive research [34]. Although from a clinical point of view, TNBCs are managed as one group, recent gene expression profiling has identified seven distinct subtypes [35]. Micro metastases are dependent on angiogenesis, suggesting that patients might benefit from antiangiogenic strategies in the adjuvant setting. However, an attempt to add bevacizumab to chemotherapy in TNBCs failed to demonstrate an advantage over the standard of care [36].

Other approaches are also being considered for TNBC: ‘Dose dense’ therapy may be a valid option based on a subgroup analysis of the CALGB9741 trial at 6 years of median follow-up [37, 38]. Moreover, the hypothesis that TNBC may benefit from platinum agents because of their reduced ability to repair DNA damage was boosted by two recent prospective randomized trials showing increased pathological complete response (pCR) from the addition of carboplatin in the neoadjuvant setting (13%–20% benefit) [39, 40]. However, there is still no consensus on the role of platinum compounds in the adjuvant setting, as it is not clear whether the incremental 20% gain in pCR would translate into improved event-free survival (EFS) or OS.

**interesting questions for the future in TNBC.** A report presented at ASCO 2013 [41] suggests that BRCA germline testing is justified in all women with TNBC under the age of 60, since, if family history or age below 50 were the only criteria used, one-third of mutation carriers would have been missed. BRCA testing in TNBC opens new options for these patients, because the inhibition of poly(adenosine diphosphate-ribose) polymerase (PARP) is a potential synthetic lethal therapeutic strategy to treat cancers with DNA-repair defects, such as those arising in patients who are carriers of BRCA1 or BRCA2 mutations [42–45].

Motivated by this idea, the Olympia study (NCT02032823) was recently launched to evaluate the role of the PARP inhibitor olaparib in treating patients with TNBC and BRCA mutations in the adjuvant setting of TNBC [46].

Another question regarding TNBC is whether metronomic chemotherapy has additive value. Results from the International Breast Cancer Study Group (IBCSG) Trial 22-00 (NCT00022516),
which randomized patients with TNBC to 1 year of continuous metronomic chemotherapy after standard chemotherapy, are eagerly anticipated. In the same context, the SYSUCC-001 trial (NCT01112826) is currently recruiting patients to address the efficacy of capecitabine (650 mg/m² for 1 year) as metronomic adjuvant chemotherapy after standard treatment.

**HER2-positive cancers**

To improve the outcome of HER2-positive BC, a dual HER2-blockade strategy consisting in the addition of lapatinib to trastuzumab was evaluated in the adjuvant setting in the ALTTO trial. Despite strong positive signals from the Neo-ALTTO study that showed a doubling of the pCR rate when the two agents are used with weekly paclitaxel before surgery [11], the combination that showed a doubling of the pCR rate when the two agents are used with weekly paclitaxel before surgery [11], the combination or the sequence of the two anti-HER2 agents failed to show improvement in DFS over trastuzumab alone in ALTTO [47]. Interestingly, in the lapatinib only arm, which was closed prematurely in view of its inability to demonstrate non-inferiority versus trastuzumab, it was shown that there was still benefit from delayed adjuvant trastuzumab therapy [48]. In another trial, BETH, the addition of bevacizumab to trastuzumab and chemotherapy also failed to improve outcomes of HER2-positive BC [49].

In an attempt to reduce treatment burden in HER2-positive patients with low risk of recurrence, Tolaney and Barry [50] enrolled 406 patients with node-negative tumors smaller than 3 cm to a single-arm study that included weekly paclitaxel plus trastuzumab for 12 weeks, followed by 9 months of trastuzumab alone. After a median follow-up of 3.6 years, only four recurrences (0.9%) were observed, suggesting that this is an attractive approach for selected patients, although a longer follow-up is desirable.

Subcutaneous trastuzumab has safety and efficacy profiles non-inferior to standard intravenous administration [51]. Moreover, subcutaneous trastuzumab was preferred by most patients that experienced both methods [52]; therefore, subcutaneous trastuzumab is emerging as a valid treatment option.

Lastly, the immune system role as prognostic or predictive biomarker in HER2-positive BC, defined by quantification of tumor lymphocytic infiltration (TILs), has recently come into focus. In the FinHer trial, which randomized patients with HER2-positive BC in the adjuvant setting to 9 weeks of trastuzumab versus no trastuzumab, the presence of TILs was associated with decreased distant recurrence in patients randomized to the trastuzumab arm, while no trastuzumab benefit was seen in the case of low TILs [53]. This suggests that TILs may be used to define patients who would derive the highest benefit from trastuzumab.

**why do we fail to incorporate new drugs in the adjuvant setting?**

Optimism about the use of pCR as a surrogate marker for efficacy in the adjuvant setting was reached when the addition of pertuzumab (Perjeta®) to the neoadjuvant treatment of patients with HER2-positive BC received conditional approval by the FDA while waiting for the results of the confirmatory phase 3 APHINITY trial [30]. This approval was also granted because of the strong positive results of the CLEOPATRA trial in the metastatic setting, which showed an impressive OS gain from the use of the two monoclonal antibodies combined with docetaxel. However, the negative results of the adjuvant ALTTO and BEATRICE trials raises broad questions about whether one can use the preoperative setting and improvement in pCR as a reliable surrogate for DFS. It was also suggested that many neo-adjuvant trials used suboptimal therapy as standard arm.

There are a few explanations about why recent clinical trials trying to incorporate new drugs failed (Table 1). Patients who participated in the ALTTO trial experienced much better outcomes than investigators initially had anticipated. The same pattern of lower than expected number of events was observed in the BETH trial. Both of these trials involved HER2-positive BC and showed excellent outcome of the standard arm, with DFS around 90%. The successes in setting-up and recruiting patients at high speed (8381 patients in 49 months in the case of

### Table 1. Possible reasons for failure of recent adjuvant breast cancer clinical trials and suggestions to improve the future trials

<table>
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<tr>
<th>Problems in breast cancer clinical trials design</th>
<th>Suggestions for the future</th>
<th>Good examples</th>
<th>Wrong examples</th>
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| Heterogeneity                                   | Predefine the subset of population that will most probably benefit from the drug | 1. HER2—trastuzumab  
2. BRCA carriers—PARP inhibitors | 1. ER and TNBC in the same trial?  
2. HER2/ER+ and HER2/ER− in the same trial? |
| Stage shifting (PET-CT), improved local and systemic management | Take action in advance to overcome stage shifting and improved local and systemic treatments | Statistical power considerations based on present practice | Statistical power considerations based on previous studies |
| Launching adjuvant trials without clear evidence of benefit in the metastatic setting | Have clear evidence of benefit in the metastatic setting | Tamoxifen, aromatase inhibitors, anthracyclines, taxanes, trastuzumab | Controversies about the efficacy of the drug in the metastatic setting |
ALTTO) [54] was found to be a double-edged sword, as no selection for high-risk patients was made (two-thirds were ER positive and 40% were node-negative), compromising the power of the trial (Figure 1).

It has recently become evident that HER2-positive cancer behaves differently depending on ER status and that crosstalk between ER and HER2 has clinical implications for endocrine and trastuzumab therapy [55]. Moreover, the tumor cancer genomic atlas using integrated analysis of different platforms clearly demonstrated that only 50% of clinically defined HER2 tumors fall into the HER2-mRNA-subtype/HER2-protein group, with the rest observed predominantly in the luminal mRNA subtypes. These data indicate that there exist at least two types of clinically defined HER2 tumors that can be easily tracked because of their ER status [56]. However, neither of the adjuvant trials (ALTTO and BETH) specifically focused on HER2-positive/ER-negative tumors, a strategy that could have been found beneficial. Indeed, in another recent publication by Goss et al., the designers of the study took advantage of the fact that, worldwide, many patients with HER2-positive BC do not receive trastuzumab, and they randomized these patients to receive lapatinib or placebo for 12 months. After a median follow-up of 4 years, in an analysis that included only centrally reviewed HER2 cancers, there was improved DFS for patients treated with lapatinib compared with placebo (HR 0.82, \( P = 0.04 \)). This effect was especially profound in ER-negative tumors (HR 0.68, \( P = 0.006 \)) [57]. This trial teaches us that drugs that fail in prospective randomized phase 3 trials actually have—or had—the potential to benefit patients, if provided in a different context.

Despite the fact that the statistical design of the mentioned trials took into account some of the issues raised above (ER and nodal status), they failed to predict the number of events correctly. This suggests that other parameters such as stage shifting, which is caused by more precise radiological examinations (for example, PET-CT) and improvement in local and systemic treatments, led to better outcome for BC patients. The fact that the TEXT and SOFT trials, which recruited a totally different population (ER-positive), missed their event plans and had to be analyzed altogether demonstrates that this shift is a general phenomenon.

Another possibility is that some of the new drugs simply do not work well enough. This may be true for lapatinib, because even in cases where an effect is seen [57], it is clearly less dramatic than the effect of trastuzumab observed more than 10 years ago [9, 10, 58]. It is also true for bevacizumab, for which three randomized trials were launched in parallel, despite the fact that the magnitude of benefit in the metastatic setting was not clear from a survival point of view [14, 15, 36].

new concepts

As novel methods develop, the future management of early BC could change dramatically. However, physicians should be careful from embracing non-evidenced-based treatments and micromanagement strategies. Studies that carried out integrated genomic analysis of thousands of specimens identified new BC clusters which may help improve future prognostication and tailored treatments [35, 59–61]. Detection of disseminated tumor cells (DTCs), circulating tumor cells (CTCs), and circulating tumor DNA are emerging as a technological advance which might enable real-time monitoring of tumor burden and may have therapeutic implications. In a recent report, marrow aspiration was carried out after chemotherapy to determine DTC status. If DTCs were present after adjuvant chemotherapy, the patient received additive docetaxel. The results showed that docetaxel-treated patients with no remaining DTCs had a similar DFS as those with no DTCs at first aspiration, which suggests that knowledge of DTC status could improve additional therapy consideration [62]. While CTC and tumor DNA are informative biomarkers in BC, currently, trials evaluating their clinical utility did not demonstrate survival advantage [63, 64]. The preoperative setting also emerges as a good platform to detect drug effectiveness during short exposure. The PeriOperative Endocrine Therapy for Individualizing Care (POETIC) trial is an example for such enterprise [65].

conclusions and recommendations

Recent decades have shown great progress with the adjuvant treatment of BC, but in the last few years, it has become difficult
to improve patient outcome using new drugs. While local procedures such as surgery and radiotherapy are becoming less invasive, systemic treatment is becoming more complex. Pharmaceutical companies are facing challenges as never before and the chance that their drugs will play an integral part of adjuvant treatment is reduced. However, there might be ways to improve the design and outcome of clinical trials (Table 1). These include (i) predefining the subset of the patient population most likely to benefit from the drug; (ii) taking action in advance to overcome stage shifting and improve treatments by calculating statistical power based on present practice and not previous studies; and (iii) having clear evidence of benefit in the metastatic setting before launching the adjuvant trial. There also appears to be a lack of imagination—or courage—to move to more to innovative clinical trial designs. Those must emerge from the academic community, which must be able to rely on improved public–private partnerships for conducting pivotal clinical trials.

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